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Advances in Biomimetic Olfactory and Gustatory Sensing Technologies (Postprint)

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Abstract

Biological olfactory and gustatory systems possess acute perception capabilities for odor and taste, and are considered among nature's most efficient sensing systems. With the advancement of human society, odor and taste sensing and detection technologies have become increasingly important for improving human quality of life and safeguarding human health, and have been widely applied in fields such as food safety, environmental monitoring, and disease diagnosis. This article reviews the development of biomimetic olfactory and gustatory sensing technologies, including electronic nose and electronic tongue chemical sensing technologies, the principles, composition, technical implementation, and applications of biomimetic olfactory and gustatory sensing technologies based on biologically sensitive materials; furthermore, it introduces research progress on novel in vivo bioelectronic noses and tongues based on brain-computer interaction; and provides an outlook on international development trends in the field of biomimetic olfactory and gustatory sensing technology.

Full Text

Preamble

The mammalian olfactory and gustatory systems possess remarkable sensitivity for detecting odors and tastants, representing one of nature's most efficient chemosensory systems. As human society advances, technologies for odor and tastant sensing have become increasingly vital for improving quality of life and safeguarding health, finding widespread applications in food safety, environmental monitoring, and disease diagnosis. This article reviews the development of bioinspired olfactory and gustatory sensing technologies, including electronic nose/electronic tongue chemical sensors, the principles, components, and technical implementation of biosensors based on biological materials, and their applications. Additionally, we introduce recent advances in novel in vivo bioelectronic

nose and tongue systems based on brain-machine interfaces and discuss future trends in the field of bioinspired olfactory and gustatory sensing technology.

Keywords: olfactory and gustatory sensing, biosensors, bioinspired sensing, brain-computer interaction, intelligent sensing

Introduction

Olfaction and gustation constitute the fundamental chemical senses through which organisms perceive environmental chemicals, providing critical support for survival, foraging, and reproduction [1,2]. Through long-term evolution, biological chemosensory systems have developed the capacity to rapidly, sensitively, and specifically detect and discriminate numerous substances in complex gaseous and liquid environments, representing one of the most effective chemical detection systems known to date. The functional components of natural olfactory and gustatory systems primarily exist at three hierarchical levels: receptors, cells, and tissues, possessing the ability to convert chemical signals carried by odorant and tastant molecules into biological signals, thus serving as natural chemical sensors [3,4]. Inspired by these natural chemosensors and driven by scientific research and practical applications, researchers have continuously proposed various biomimetic olfactory and gustatory sensing systems employing chemical and biological materials.

Bioinspired olfactory and gustatory sensors consist primarily of two components: biological functional elements and micro/nano transducers. The biological functional elements serve as sensitive components that bind target molecules or ions and generate specific responses, while micro/nano transducers convert these responses into more easily processed and analyzed physical signals such as optical or electrical signals [5]. In recent years, as research into the biological mechanisms of olfaction and gustation has deepened, biomimetic sensors have achieved breakthrough progress and begun to emerge in both fundamental research and practical applications. Compared with traditional gas and liquid chromatography instruments, olfactory and gustatory biomimetic sensors inherit the advantages of biological chemosensory systems, demonstrating superior performance in sensitivity, response time, and specificity, and showing broad application prospects in food safety, environmental monitoring, and disease detection [6,7].

Biomimetic Sensing Based on Olfactory and Gustatory Cells

Cell-based biosensors utilize living cells as sensitive elements to detect functional information about bioactive substances. Consequently, many studies have employed primary olfactory sensory neurons (OSNs) and gustatory receptor cells as sensitive materials in developing olfactory and gustatory biomimetic sensors. We combined primarily cultured OSNs with a light-addressable potentiometric sensor (LAPS). When specific receptors on the OSN membrane surface bind odorant molecules, they induce changes in intracellular and extracellular ion

concentrations [Figure 3a: see original paper], ultimately affecting the bias current of the LAPS sensor, enabling detection of different odorant molecules [13]. This system can also monitor cell status. Additionally, using LAPS, we tested OSN responses to the inhibitor MDL12330A and the agonist LY294002, with results consistent with biological methods [Figure 3b: see original paper] [14]. We also coupled primary taste cells with LAPS to propose a non-invasive method for studying intercellular signal transduction mechanisms within taste buds [15].

Building upon the use of primary olfactory and gustatory cells as biomimetic sensitive elements, we proposed a heterologous expression cell-based gustatory biosensor that transfects human olfactory or gustatory receptors into established cell lines. The introduction of human receptors enables better simulation of human chemosensation. For example, we transfected human T2R14 bitter receptors and G α 16 protein into human embryonic kidney (HEK-293) cells and cultured these receptor-transfected HEK-293 cells on an electric cell-substrate impedance sensor (ECIS) surface, enabling specific detection of ligands such as salicin [16]. Research has shown that taste receptors are widely expressed in many non-gustatory tissues and cells, including gastrointestinal cells, organ epithelial cells, and mouse germ cells. Consequently, we also developed a bitter substance detection system based on mouse germ cells and ECIS sensors, enabling quantitative detection of multiple bitter substances [17].

Biomimetic Sensing Based on Olfactory and Gustatory Receptor Proteins

The foundation of biological recognition of odorant and tastant molecules lies in the receptors located on the cilia of olfactory and gustatory receptor cells. Therefore, researchers have proposed biosensors based on olfactory and gustatory receptors, where receptor activity critically affects sensor performance. Olfactory receptors are hydrophobic G protein-coupled receptors (GPCRs) whose seven transmembrane domains require cell membrane support, making the development of receptor-based olfactory biomimetic sensors a significant current challenge.

To address this issue, we investigated direct extraction of olfactory receptors from primary olfactory tissue for use as sensitive elements immobilized on sensor surfaces. We isolated olfactory proteins from bullfrog olfactory epithelium and modified sensor surfaces with them for detection of various volatile organic compounds [18]. Other researchers have proposed using heterologous expression systems, coupling cell membranes bearing olfactory receptors with transducers to construct olfactory biomimetic sensors. The most commonly used heterologous expression systems include HEK-293 cells, human breast cancer MCF-7 cells, and fungi [5]. We investigated a biomimetic olfactory sensor based on a surface acoustic wave (SAW) sensor and the *E. coli* olfactory receptor ORD-10 [Figure 4: see original paper] [19].

Insect odorant recognition requires the participation of odorant binding proteins

(OBPs). OBPs bind hydrophobic odorant molecules, enhance their hydrophilicity, and transport them to specific binding sites on receptors. OBPs possess sensitivity and specificity comparable to olfactory receptors but have simpler structures. Lu et al. [20] immobilized honeybee OBPs on impedance chip surfaces to specifically detect pheromones, and this system could also be used to study other functions of OBPs.

Similar to olfactory receptors, bitter, sweet, and umami taste receptors are also GPCRs, making the development of biomimetic sensors based on these receptors equally challenging. Song et al. [21] expressed the human taste receptor heterodimer hT1R2+hT1R3 on HEK-293 cell membranes, shattered the cells into nanovesicles bearing taste receptors, and immobilized them on a field-effect transistor (FET) sensor surface, providing a novel sensing technology for sweet substance detection. However, sour and salty receptors are ion channel-type receptors, and no biomimetic taste sensors based on these receptors have yet been constructed.

A quartz crystal microbalance (QCM)-based gustatory biomimetic sensor structure is shown in [Figure 5a: see original paper] [22]. We expressed the human bitter receptor hT2R4 on HEK-293 cell membranes, labeled the receptor C-terminus with a His6 tag, and used a kit to disrupt cells and extract cell membrane fragments containing hT2R4 receptors. Meanwhile, the QCM surface was functionalized with thiol-modified anti-His6 tag aptamers that could specifically capture His6-tagged hT2R4 receptors, accurately immobilizing membrane fragments on the device surface [Figure 5b: see original paper]. The presence of the phospholipid bilayer maintains the receptor's transmembrane structure, potentially helping to solve issues of immobilization efficiency and distribution density. Testing this QCM-based gustatory biomimetic sensor demonstrated effective detection of the bitter substance denatonium within a certain concentration range, showing high specificity and sensitivity for specific bitter substances.

In Vivo Bioelectronic Nose and Tongue Based on Brain-Machine Interaction

While ex vivo cell and molecular olfactory/gustatory sensors utilize tissue culture and microfabrication technologies to culture olfactory/gustatory-sensitive neurons, tissues, or proteins on sensor chip surfaces for rapid, sensitive, and specific chemical detection, in vitro culture cannot guarantee long-term viability of biological materials, affecting sensor lifespan and preventing long-term repeated detection. Furthermore, ex vivo culture disrupts the integrity of the olfactory/gustatory system, altering normal neuronal response patterns. Therefore, scientists have begun exploring how to utilize intact biological olfactory and gustatory systems for gas or tastant detection to improve sensor lifespan.

With the development of brain-machine interface technology, our team proposed a novel in vivo olfactory and gustatory sensing technology that directly utilizes the intact biological chemosensory system [8,9]. By decoding neuronal activ-

ity patterns in the brain responsible for chemical information processing and constructing mapping models between neuronal activity patterns and chemical stimuli, detection and identification of odorant and tastant molecules can be achieved.

In Vivo Bioelectronic Nose

Utilizing implantable neural signal recording technology, our team proposed a novel in vivo bioelectronic nose [Figure 6: see original paper]. Mammalian olfactory epithelium serves as the primary odorant receptor, generating response signals that are processed and modified in the olfactory bulb and olfactory cortex. Implantable microelectrode arrays were embedded in the olfactory bulb to simultaneously record signals from multiple mitral/tufted cells. Through pattern recognition algorithms, neuronal signals were decoded to extract odor-related information, enabling odor detection. Combining maximum likelihood estimation and principal component analysis methods, we found that the in vivo bioelectronic nose could effectively discriminate single-molecule odors with different functional groups, including carvone, butanedione, anisole, isoamyl acetate, octanol, valeraldehyde, and butyric acid, with 92.67% accuracy [26]. The system could also effectively distinguish mixed odors released by bananas, oranges, strawberries, and pineapples [8]. The minimum detectable concentration for carvone reached below 10^{-10} mol/L, with a service life of up to 3 months.

In Vivo Bioelectronic Tongue

In the mammalian gustatory system, tastants bind to taste buds on the tongue surface, and signals are transmitted through gustatory nerve fibers via the brainstem, amygdala, and thalamus to the gustatory cortex. Similar to the in vivo bioelectronic nose, our team extracted neuronal responses from the mammalian gustatory cortex to sweet, salty, sour, and bitter substances. By combining local field potential (LFP) and single-neuron action potential (spike) signal features from the gustatory cortex, we effectively discriminated sucrose (sweet), sodium chloride (salty), hydrochloric acid (sour), and denatonium benzoate (bitter), showing concentration-dependent responses for sweet and bitter substances. The minimum detectable concentration for denatonium benzoate reached 7.6×10^{-8} mol/L [9] [Figure 7: see original paper]. Furthermore, using support vector machine methods, we effectively distinguished three bitter substances—denatonium benzoate, quinine, and salicin—with 94.05% accuracy [27].

Our team also conducted in-depth analysis of the detection performance of in vivo bioelectronic noses and tongues regarding service life, repeatability, specificity, and sensitivity, demonstrating their unique advantages and capabilities for odor and tastant detection. We are currently expanding the sample size for odor and tastant detection and further improving artificial neural network recognition algorithms to advance the development of in vivo bioelectronic noses and tongues.

Applications of Bioinspired Olfactory and Gustatory Sensing Technology

After years of development, biomimetic electronic noses and tongues have been widely applied in the food and perfume industries, environmental quality monitoring, and biomedical fields [28]. Although the new generation of ex vivo molecular and cellular olfactory and gustatory sensors started later, their detection performance has been repeatedly validated at the laboratory stage and is gradually entering application testing phases. The main application areas include the following four aspects.

Food Quality Detection

In the food industry, applications include raw material quality inspection, processing supervision, and food freshness detection. During storage, food inevitably deteriorates, and detecting gases, enzymes, and microorganisms produced during spoilage provides an effective means to predict shelf life. For example, Lim et al. [29] used a biomimetic electronic nose to monitor seafood quality in real time.

Drug and Explosive Detection

Drugs and their packaging materials generally have characteristic odors that can be identified from gas and taste signatures without human tasting, enabling rapid on-site identification. Since characteristic odors from drugs and packaging materials are typically present at low concentrations, there is a need to develop rapid, highly sensitive, and specific biomimetic olfactory and gustatory sensors and instruments. Explosives generally contain negatively charged nitrogen and oxygen as oxidizers during combustion, with most high-energy explosives using nitrates as oxidizers. Analysis of nitrogen/oxygen components and characteristic gases can effectively enable explosive detection [30].

Medical Diagnosis

In 1971, Pauling et al. [31] first proposed that volatile organic compounds (VOCs) exist in human exhaled breath. Healthy human breath contains approximately 200 VOCs with very complex composition, some at extremely low concentrations (10^{-12} mol/L). Gordon et al. [32] proposed that exhaled breath from lung cancer patients contains characteristic VOCs (biomarkers) such as acetone, methyl ethyl ketone, n-propanol, and styrene that differ from healthy individuals. Therefore, highly sensitive and specific detection of these characteristic VOCs could enable early lung cancer diagnosis.

Environmental Monitoring

Air quality issues have received increasing attention in recent years, as air pollution significantly impacts the environment and human health. Worldwide, 3-

7 million deaths annually result from cardiopulmonary diseases caused by particulate matter (PM). PM is primarily generated by power plants, industrial enterprises, vehicles, and combustion of biomass fossil fuels. To address these health concerns, many countries have developed on-site rapid detection technologies for carbon monoxide, nitrogen monoxide, nitrogen dioxide, ozone, benzene, toluene, and xylene, which have been applied in various settings .

With rapid international development of sensor technology and MEMS, olfactory and gustatory biomimetic sensing technologies have enabled detection of specific odors and tastants through chemical and biological sensors based on different transduction principles. Although they cannot yet replace complex chemical analysis equipment, biomimetic sensors have been widely adopted in daily life due to advantages in portability, operational simplicity, and cost. With advances in life sciences, the new generation of olfactory and gustatory biomimetic sensing technology that replaces chemical sensors with biological sensitive materials better leverages biological superiority, compensating for limitations of electronic noses and tongues in response speed, sensitivity, and specificity. By harnessing the sophisticated sensing capabilities of biological olfactory and gustatory systems and combining them with engineering techniques for biological signal analysis and recognition, these technologies transform biological signals into readable detection information, developing a new generation of intelligent olfactory and gustatory sensing systems that will further advance the field.

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